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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/873,286	REID ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-47 and 49-51* is/are rejected.

7)☒ Claim(s) *48* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *attached hereto*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 5/26/04 is acknowledged and has been entered.

2. In view of Applicant's said amendment, prosecution is hereby REOPENED.

3. The terminal disclaimer filed on 5/26/04 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent Serial No. 6,069,005 has been reviewed and is accepted. The terminal disclaimer has been recorded.

4. The terminal disclaimer filed on 5/26/04 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of U.S. Patent Serial No. 6,242,252 has been reviewed and is accepted. The terminal disclaimer has been recorded.

5. It is noted by the Examiner that Applicant has indicated that the monoclonal antibodies OX-43 and OX-44 are readily available to the public from Serotec Corporation of Indianapolis.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 35, 37-39, 42-47, 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoang et al (Blood 1983, 61(3): 580-588, IDS reference) in view of Hixson et al (Pathobiology 1990, 58: 65-77, IDS reference), Germain et al (Cancer Res. 1988, 48: 4909-4918, IDS reference) and Alberts et al (Molec. Biol. Cell. 2nd Ed., 1989, page 159).

Hoang et al teach a method of isolating hematopoietic progenitor cells from bone marrow using monoclonal antibodies (mAb) and panning combined with fluorescence activated cell sorting (FACS). Hoang et al teach performing a negative selection by panning using a mAb which binds most end-stage marrow cells including red cells, B cells, neutrophils and monocytes. Hoang et al teach a FACS procedure using mAb to the end-stage marrow cells and light scatter to differentiate the progenitor cells from the mature hematopoietic cells. Hoang et al teach that the initial panning procedure is used to remove large numbers of nucleated red cells (immature red cells), lymphocytes and neutrophils. Hoang et al teach that any undesired cells remaining after panning are removed by the FACS procedure, and that the combination of panning and FACS achieved a great enrichment in colony-forming cells as well as a segregation of early and late progenitors. Hoang et al teach that the main advantage of panning is that it allows a

large number of cells to be handled, an advantage that is especially useful when isolating rare cell types (especially pages 580, 581, 586 and 587).

Hoang et al do not teach enriching or isolating hepatic progenitors.

Hixson et al teach that liver stem cells are postulated to be involved in carcinogenesis. Hixson et al teach use of mAb against adult hepatocytes and oval cell antigens, the latter cells being a phenotypically complex cell compartment composed of at least three distinct antigenic subtypes, one subtype closely resembling antigenically primitive cell populations in the fetal liver and presumed to be facultative liver stem cells that are malignantly transformed. Hixson et al teach that fetal hepatoblasts express the oval cell antigen OC.3 recognized by mAb 374.3, but express few hepatocyte antigens. Hixson et al teach use of mAbs link a primitive cell type present in embryonic liver to both a ductal and hepatocyte differentiation pathway and provide strong evidence that many chemically induced hepatocellular carcinomas are derived via a pathway involving carcinogen interaction with facultative stem cell targets still present in adult liver. Hixson et al point out that much of what we know regarding T cell and B cell differentiation has been derived from analysis of large panels of lymphoid tumor lines which have phenotypes representative of cells arrested in particular stages in normal differentiation. Hixson et al teach that *if* oval cell phenotypes are representative of normal states of differentiation, then one must postulate the existence of an $OC.3^+$ bipotential cell which persists in adults (especially pages 65-69). Hixson et al teach the presence of $OC.3^+$ cells in normal fetal liver and in neonatal liver up to 14 days post-partum, however, Hixson et al each that after day 14 post-partum, the level of $OC.3^+$ cells decreases to adult levels due primarily to the decrease in the number of myeloid cells.

Germain et al teach analysis of fetal liver cells. Germain et al teach isolation of liver cells, i.e., single cell suspensions, using medium containing collagenase to digest the liver tissue. Germain et al teach the presence of a population of bipotential hepatic progenitors that give rise to biliary ductular cells as well as to hepatocytes in fetal liver. Germain et al teach mAb that react specifically with biliary epithelial cells or with hepatocytes (especially pages 4909-4918).

Alberts et al teach that the first step in isolating cells of a uniform type from a tissue that contains a mixture of cell types is to reduce the tissue to a suspension of single cells. Alberts et al teaches that this is done by disrupting the extracellular matrix and intracellular junctions that hold the cells together, and that the best yields of viable dissociated cells are obtained from fetal or neonatal tissues, typically by treating them with proteolytic enzymes such as trypsin and collagenase and with agents that bind or chelate calcium such as EDTA on which cell-to-cell adhesion depends. Alberts et al teaches panning to remove certain cell populations using specific mAb, and also by FACS (especially page 159).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have prepared a single cell suspension of fetal or neonatal liver cells as per the teaching of Germain et al and Alberts et al, and to have enriched for hepatic progenitors using the method taught by Hoang et al and Alberts et al of panning and FACS using mAbs taught by Hoang et al to negatively enrich by removing hematopoietic cells and hepatocytes, and to positively select using the mAb 374.3 taught by Hixson et al that recognizes the OC.3 antigen expressed on fetal hepatoblasts or on neonatal liver cells up to day 14 post-partum.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to enrich for liver hepatic progenitor cells because Hoang et al teach that the preparation of single cell suspensions via treatment with proteases and that the combination of panning and FACS provides a good isolation of stem cells, Alberts et al teach the first step in isolating cells of a uniform type from a tissue that contains a mixture of cell types is to reduce the tissue to a suspension of single cells and that the highest yields are obtained from fetal or neonatal tissues and the combination of panning and FACs to remove certain cell populations, and Hixson et al and Germain et al teach that fetal liver contains biopotent hepatic progenitors that differentiate into the ductal and hepatocyte differentiation pathways, and Hoang et al teaches that panning combined with FACS achieves separation of rare cells. Claim 36 is included in this rejection because mesenchymal cells comprise endothelial cells. Claims 44 and 45 are included in this rejection because it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have chilled the single cell suspension at 4 degrees C in order to inhibit the activity of endogenous proteases present in the single cell suspension and to inhibit surface antigen internalization and turnover, and further because Hoang et al teach panning at 4 degrees C.

8. Claims 36 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoang et al (Blood 1983, 61(3): 580-588, IDS reference) in view of Hixson et al (Pathobiology 1990, 58: 65-77, IDS reference), Germain et al (Cancer Res. 1988, 48: 4909-4918, IDS reference) and Alberts et al (Molec. Biol. Cell. 2nd Ed., 1989, page 159) as applied to claims 35, 37-39, 42-47, 50 and 51 above, and further in view of Robinson et al (Immunology 1986, 57: 231-237, IDS reference).

Hoang et al, Hixson et al, Germain et al and Alberts et al have been discussed supra, hereafter "the combined references". In addition, the studies taught by Hixson et al were conducted with rat liver and Hixson et al teach the presence of epithelial cells in the liver.

The combined references do not teach the method wherein the monoclonal antibody specific for hematopoietic cells is OX-43.

Robinson et al teach mAb OX-43 reacts with vascular endothelium in the rat as well as with erythrocytes and some macrophage populations and that OX-43 is suitable for use in FACS.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the OX-43 mAb taught by Robinson et al in the method of the combined references for negative selection.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to remove erythrocytes from the single cell preparation as well as to remove endothelial cells from the liver cell suspension of Germain et al because Robinson et al teach that OX-43 reacts with erythrocytes as well as with endothelial cells and Hixson et al teaches the presence of epithelial cells in the liver and Hoang et al teach that negative selection is used to remove the contaminating cells that are present in large numbers prior to positive selection, and Alberts et al teach removal of certain cells by panning using mAbs.

9. Claims 35, 37-40, 42-47, 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bodger (Exp. Hematol. 1987,15: 869-876, IDS reference) in view of Hixson et al (Pathobiology 1990, 58: 65-77, IDS reference), Germain et al (Cancer Res. 1988, 48: 4909-4918, IDS reference) and Alberts et al (Molec. Biol. Cell. 2nd Ed., 1989, page 159).

Bodger teaches a method of isolating hematopoietic progenitor cells from umbilical cord blood and from fetal liver using monoclonal antibodies (mAb) and panning combined with fluorescence activated cell sorting (FACS). Bodger teaches performing a negative selection by using a panel of mAbs to deplete mature and immature myeloid and lymphoid cells. Bodger teaches a FACS procedure using mAb and light scatter. Bodger teaches that the initial panning procedure is used to remove large numbers of adherent cells. Bodger teaches that the combination of panning, negative selection and FACS achieved a substantial enrichment of their target cell population. Bodger teaches that of several immunological techniques used to isolate progenitor cells from human hemopoietic tissue, negative selection by immune-panning has resulted in the greatest enrichment of progenitor cells. Bodger teaches washing the cord blood cells in a solution containing tetrasodium EDTA, i.e., a calcium chelator (especially pages 869-876).

Bodger does not teach enriching or isolating hepatic progenitors.

Hixson et al teach that liver stem cells are postulated to be involved in carcinogenesis. Hixson et al teach use of mAb against adult hepatocytes and oval cell antigens, the latter being presumed to be the liver stem cells that are malignantly transformed, and the latter closely resembling antigenically primitive cell populations in the fetal liver. Hixson et al teach that fetal hepatoblasts express the oval cell antigen OC.3 recognized by mAb 374.3, but express few hepatocyte antigens. Hixson et al teach use of mAbs link a primitive cell type present in embryonic liver to both a ductal and hepatocyte differentiation pathway and provide strong evidence that many chemically induced hepatocellular carcinomas are derived via a pathway

Hixson et al teach that liver stem cells are postulated to be involved in carcinogenesis. Hixson et al teach use of mAb against adult hepatocytes and oval cell antigens, the latter cells being a phenotypically complex cell compartment composed of at least three distinct antigenic subtypes, one subtype closely resembling antigenically primitive cell populations in the fetal liver and presumed to be facultative liver stem cells that are malignantly transformed. Hixson et al teach that fetal hepatoblasts express the oval cell antigen OC.3 recognized by mAb 374.3, but express few hepatocyte antigens. Hixson et al teach use of mAbs link a primitive cell type present in embryonic liver to both a ductal and hepatocyte differentiation pathway and provide strong evidence that many chemically induced hepatocellular carcinomas are derived via a pathway involving carcinogen interaction with facultative stem cell targets still present in adult liver. Hixson et al point out that much of what we know regarding T cell and B cell differentiation has been derived from analysis of large panels of lymphoid tumor lines which have phenotypes representative of cells arrested in particular stages in normal differentiation. Hixson et al teach that *if* oval cell phenotypes are representative of normal states of differentiation, then one must postulate the existence of an $OC.3^+$ bipotential cell which persists in adults (especially pages 65-69). Hixson et al teach the presence of $OC.3^+$ cells in normal fetal liver and in neonatal liver up to 14 days post-partum, however, Hixson et al each that after day 14 post-partum, the level of $OC.3^+$ cells decreases to adult levels due primarily to the decrease in the number of myeloid cells.

Germain et al teach analysis of fetal liver cells. Germain et al teach isolation of liver cells, i.e., single cell suspensions, using medium containing collagenase to digest the liver tissue. Germain et al teach the presence of a population of bipotential hepatic progenitors that give rise to biliary ductular cells as well as to hepatocytes in fetal liver. Germain et al teach mAb that react specifically with biliary epithelial cells or with hepatocytes (especially pages 4909-4918).

Alberts et al teach that the first step in isolating cells of a uniform type from a tissue that contains a mixture of cell types is to reduce the tissue to a suspension of single cells. Alberts et al teaches that this is done by disrupting the extracellular matrix and intracellular junctions that hold the cells together, and that the best yields of viable dissociated cells are obtained from fetal or neonatal tissues, typically by treating them with proteolytic enzymes such as trypsin and collagenase and with agents that bind or chelate calcium such as EDTA on which cell-to-cell adhesion depends. Alberts et al teaches panning to remove certain cell populations using specific mAb, and also by FACS (especially page 159).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have prepared a single cell suspension of fetal or neonatal liver cells as per the teaching of Germain et al and Alberts et al, and to have enriched for hepatic progenitors using the method taught by Bodger of panning and FACS and by Alberts et al using mAbs taught by Bodger or by Germain et al to negatively enrich by removing hematopoietic cells and hepatocytes, and to positively select using the mAb 374.3 taught by Hixson et al that recognizes the OC.3 antigen expressed on fetal or neonatal hepatoblasts.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to enrich for liver hepatic progenitor cells because Alberts et al teach the first step in isolating cells of a uniform type from a tissue that contains a mixture of cell types is to reduce the tissue to a suspension of single cells and combination of panning and FACs to remove certain cell populations, Bodger teaches that the combination of panning and FACS provides a good enrichment of progenitor cells, and Hixson et al and Germain et al teach that fetal liver contains biopotent hepatic progenitors that differentiate into the ductal and hepatocyte differentiation pathways, and Bodger teaches that panning combined with FACS achieves superior isolation of target cell populations. Claim 36 is included in this rejection because mesenchymal cells comprise endothelial cells. Claims 44 and 45 are included in this rejection because it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have chilled the single cell suspension at 4 degrees C in order to inhibit the activity of endogenous proteases present in the single cell suspension and to inhibit surface antigen internalization and turnover, and further because Bodger teaches incubation with mAb at 4 degrees C. Claim 46 is included in this rejection because Alberts et al teach that the best yields of viable dissociated cells are obtained from fetal or neonatal tissues.

10. Claims 36 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bodger (Exp. Hematol. 1987,15: 869-876, IDS reference) in view of Hixson et al (Pathobiology 1990, 58: 65-77, IDS reference), Germain et al (Cancer Res. 1988, 48: 4909-4918, IDS reference) and Alberts et al (Molec. Biol. Cell. 2nd Ed., 1989, page 159) as applied to claims 35, 37-40, 42-47, 50 and 51 above, and further in view of Robinson et al (Immunology 1986, 57: 231-237, IDS reference).

Bodger, Hixson et al, Germain et al and Alberts et al have been discussed supra, hereafter "the combined references". In addition, the studies taught by Hixson et al were conducted with rat liver and Hixson et al teach the presence of epithelial cells in the liver.

The combined references do not teach the method wherein the monoclonal antibody specific for hematopoietic cells is OX-43.

Robinson et al teach mAb OX-43 reacts with vascular endothelium in the rat as well as with erythrocytes and some macrophage populations and that OX-43 is suitable for use in FACS.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the OX-43 mAb taught by Robinson et al in the method of the combined references for negative selection.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to remove erythrocytes from the single cell preparation as well as to remove endothelial cells from the liver cell suspension of Germain et al because Robinson et al teach that OX-43 reacts with erythrocytes as well as with endothelial cells and Hixson et al teach the

presence of epithelial cells in the liver and Bodger teaches that negative selection is used to remove the contaminating cells that are present in large numbers prior to positive selection and Alberts et al teach preparation of single cell suspensions from fetal and neonatal tissue and removal of cell types by panning with mAb.

11. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bodger (Exp. Hematol. 1987,15: 869-876, IDS reference) in view of Hixson et al (Pathobiology 1990, 58: 65-77, IDS reference), Germain et al (Cancer Res. 1988, 48: 4909-4918, IDS reference) and Alberts et al (Molec. Biol. Cell. 2nd Ed., 1989, page 159) as applied to claims 35, 37-40, 42-47, 50 and 51 above, and further in view of Stryer (Biochemistry 3rd Ed., 1988, page 990).

Bodger, Hixson et al, Germain et al and Alberts et al have been discussed supra, hereafter "the combined references".

The combined references do not teach the method wherein the single cell suspension comprises EGTA.

Stryer teaches EGTA specifically binds to calcium with high affinity.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used EGTA in place of EDTA because Alberts teaches use of calcium chelator EDTA and Stryer teaches EGTA is also a calcium chelator that specifically binds calcium with high affinity.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to provide a calcium chelator that binds calcium with high affinity.

12. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hoang et al (Blood 1983, 61(3): 580-588, IDS reference) in view of Hixson et al (Pathobiology 1990, 58: 65-77, IDS reference), Germain et al (Cancer Res. 1988, 48: 4909-4918, IDS reference) and Alberts et al (Molec. Biol. Cell. 2nd Ed., 1989, page 159) as applied to claims 35, 37-39, 42-47, 50 and 51 above, and further in view of Stryer (Biochemistry 3rd Ed., 1988, page 990).

Hoang et al, Hixson et al, Germain et al and Alberts et al have been discussed supra, hereafter "the combined references".

The combined references do not teach the method wherein the single cell suspension comprises EGTA.

Stryer teaches EGTA specifically binds to calcium with high affinity.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used EGTA in place of EDTA because Alberts teaches use of calcium chelator EDTA and Stryer teaches EGTA is also a calcium chelator that specifically binds calcium with high affinity.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to provide a calcium chelator that binds calcium with high affinity.

13. Claim 48 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

14. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Wednesday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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